REMARKS

Claims 13 and 34 have been cancelled. Claim 1 and 16 have been amended to incorporate the feature of claim 13 and to more clearly define the invention. Claim 37 has been added directed to antibiotics which are listed in claim 15. Claim 38 has been added directed to supersaturated solutions which are mentioned at page 6, line 30 to page 7, line 2.

Claims Rejection - 35 U.S.C. § 112

Claims 14-15 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Office Action considers that the wording of claim 14 is unclear as to how the encapsulated pharmaceutically active agent can assist the binding of the vesicle. Claim 14 has been amended to include language having a basis at page 2, line 28 of the specification. Once the calcium phosphate in the outer layer has bound to the bone then the pharmaceutically active compound will be released to assist in further binding of the outer layer to bone.

It is believed, therefore, that the rejection under § 112 has been overcome.

Claim Rejections 35 U.S.C. §102 and § 103

Claims 1-2, 6, 10, 16, 21-23 and 34 stand rejected under 35 U.S.C. 102(b) as being anticipated by Eanes (Bone and Mineral 17, pp. 269-272, 1992) or Eanes (Calcif. Tissue Int (40 pp. 43-48, 1987), while claims 7-12 stand rejected under 35 U.S.C. 103(a) as unpatentable over the two Eanes references. Since claim 13 is not rejected on these grounds and claim 13 has been incorporated into claim 1, the rejections are

moot. It is believ d that the same applies to claims 16, 21-23 and 34 now that claim 16 incorporates the feature of claim 13.

In paragraph 7 of the Office Action, claims 1-2, 6-16, 21-24, 26-29 and 31-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over EP-0-479,582 of record in combination with either of Eanes and Chung (US-5,039,546). The Office Action states that EP 0-479,582 discloses multi-laminar liposomes containing an antibiotic, these liposomes being suspended in hydroxyapatite for use with dental implants. The Office Action states that what is lacking in EP 479,582 is a teaching of coating the liposomes with apatite (calcium phosphate) instead of hydroxyapatite and also the attachment of the liposomes to a surface. The Office Action believes that these are made good by the Eanes articles which are concerned with the formation of calcium phosphate and by Chung which discloses that for dental implants one can coat with either hydroxyapatite or calcium phosphate. The Office Action concludes, therefore, that it would have been obvious to replace hydroxyapatite by calcium phosphate in EP 479,582 and that the coating of substrate would have been obvious in view of Chung although the Office Action admits that Chung does not disclose specifically the sizes of the implants.

The Office Action points out that EP 479,582 does mention bone generation in the abstract. However, it is clear that the material of EP 479,582 is entirely different from applicant's vesicles and, indeed, those of Eanes. Effectively, EP 479,582 discloses vesicles containing a pharmaceutical which are mixed with a slurry of hydroxyapatite and collagen. Thus at page 4, lines 26 to 28 it is stated that the "present invention is a ..... system employing multi-lamellar liposomes having multiple encapsulating layers of

aqueous dissolved antibiotic mixed in suspension with hydroxyapatite and collagen (emphasis added)". Further confirmation of this is provided at e.g. page 6, lines 4 to 12. Thus although the end product contains calcium phosphate as well as vesicles there is no individual entity which has both these features. In contrast, applicant is concerned with individual vesicles which possess calcium phosphate as an outside layer formed on an inner layer of a phospholipid and which contain a pharmaceutically active compound within the vesicle. These are therefore completely different.

A consequence of applicant's vesicles is that they can readily be tailored to regulate diffusion in a way which is not possible by the EP 479,582 arrangement. Thus a change in vesicle breakdown can readily be achieved by varying the size of the vesicle or, changing the liposome, the thickness of the calcium phosphate layer or the stoichiometry of the calcium phosphate used. This can be done on an individual vesicle basis.

It is believed, therefore, that EP 479,582 is lacking in very much more than the teaching of the coating of the liposomes with apatite rather than hydroxyapatite. Indeed there is no coating of the vesicles at all (although in the mixture the vesicles will come into contact with calcium phosphate in the paste or slurry).

In general, applicants' vesicle will not contain calcium phosphate in the interior or chamber of the vesicle. This is because applicant's process involves calcifying the already formed vesicle. In contrast, Eanes requires the interior of the vesicle to be filled with calcium phosphate. This serves a particular purpose for Eanes and arises out of the fact that Eanes suggests in several places that it is not possible to prepare vesicles

of the type claimed by applicant. Thus at the top of the left-hand column on page 44 (Calcified Tissue article), Eanes states "the apparent inability of ... liposomes themselves to seed metastable calcium phosphate solutions...". Of course applicant's vesicles are prepared by depositing calcium phosphate on the liposomes.

At page 46, right-hand column, lines 17 to 22 Eanes states that "even if the PS molecules were clustered into coherent domains on the outer liposomal surface, they probably would not have established suitable substrates for mineral nucleation at the solution supersaturations employed."

Page 47, left-hand column, lines 18 to 23 says that "such extraliposomal precipitation was brought about primarily by the seeding action of intraliposomal apatite crystals that had worked their way through the outer membranes into the external solution". Clearly, therefore, there is no contemplation here that one can precipitate calcium phosphate directly on the outside of the vesicles.

Finally, page 47, right-hand column lines 23 to 27 again stresses that the "first mineral particles occur adjacent to the interior membrane leaflet of matrix vesicles".

The presence of calcium phosphate in the chamber of the vesicle of Eanes serves the express purpose of initiating the formation of calcium phosphate on the outside of the vesicles. This becomes apparent from the passage at page 47 of the Calcified Tissue article, left hand column, line 18 to 23 quoted above but is confirmed by the Bone and Mineral article which states (at the foot of page 269) that "..... mineral eventually forms outside the liposomes as well. This latter location is seeded by intra liposomally-formed crystals which penetrate the membrane". Again on page 271 it is stated " although the mechanism by which crystals penetrate the membrane to initiate

extra liposomal precipitation is unknown ....". Applicants do not require this seeding of calcium phosphate which penetrates the vesicle membrane.

This difference is a very significant one because the fact that calcium phosphate crystals work their way through the vesicle wall in Eanes makes it clear that the walls are ruptured. A consequence of this is that if, for the sake of argument, one places pharmaceutically active material in the vesicles (although Eanes does not suggest this) it would soon leak out. Stated differently, if one were to place a pharmaceutically active material in the vesicles (as stated in EP 0 479 582) and try to form an outer layer of calcium phosphate on the vesicles using the Eanes methods, the vesicles would be punctured thereby allowing the pharmaceutically active material to leak out. Thus, the vesicles of Eanes are entirely unsuited for use as carriers for pharmaceutically active compounds. Thus if, for the sake of argument, one were to combine EP 0 479 582 with Eanes one would arrive at a product which plainly would not work. This is confirmed by the accompanying declaration by inventor Czernuszka. Attention is also directed to M.P.E.P. 2143.01 wherein it is stated that "if [a] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification" (*citing In re Gordon*, 733 F.2d 900, 221 USPQ 1125, Fed. Cir. 1984).

Accordingly, applicants' vesicles, as recited in amended claim 1, which require containing a pharmaceutically active compound in the vesicle, are clearly patentable over EP 0 479 582 in combination with Eanes.

The rejection also refers to Chung (US-5,039,546). This is on the basis that Chung discloses that for dental implant one can coat with ither hydroxyapatite or

calcium phosphate. This is clearly true but does not take the argument any further. This is because Chung does not make up for the deficiencies in Eanes or those of EP 0 479 582.

The remaining references fail to make up for the deficiencies in Eanes and EP 479,582.

In summary, it is believed that amended claim 1 (and claims 2, 6-12, 14-16, 18-23, 26-30 and 35-38 that depend thereon) are patentable over the prior art of record.

Conclusion

It is submitted that the application has been placed in condition for allowance.

No other fees are believed to be needed for this amendment. However, if additional fees are needed, please charge them to Deposit Account No. 17-0055.

Respectfully submitted,
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